

*Citation for published version:*

Bent, SJ, Mahon, MF & Webster, RL 2015, 'Copper malonamide complexes and their use in azide-alkyne cycloaddition reactions', *Dalton Transactions*, vol. 44, no. 22, pp. 10253-10258.  
<https://doi.org/10.1039/C5DT01312G>

*DOI:*

[10.1039/C5DT01312G](https://doi.org/10.1039/C5DT01312G)

*Publication date:*

2015

*Document Version*

Peer reviewed version

[Link to publication](#)

## University of Bath

### Alternative formats

If you require this document in an alternative format, please contact:  
[openaccess@bath.ac.uk](mailto:openaccess@bath.ac.uk)

#### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

#### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

# Copper malonamide complexes and their use in azide-alkyne cycloaddition reactions

S. J. Bent, M. F. Mahon and R. L. Webster\*

Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

We report a rare example of the malonamide functionality being used as a ligand in copper catalysis. We have ligated a homologous series of these *O,O*-chelating architectures to copper, investigated their structure and exploited them in azide-alkyne cycloaddition reactions for the step-growth synthesis of oligo(triazoles) and in the synthesis of small organic azoles.

## Introduction

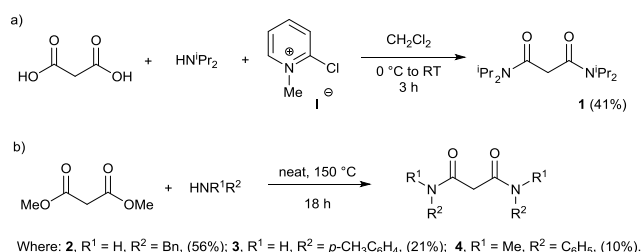
The development of new ligands is an important undertaking in synthetic chemistry, providing access to untapped facets of classical coordination chemistry and providing us with the opportunity to enhance known catalytic transformations or even to develop entirely new catalytic reactions. The malonamide motif is known to act as an *O,O*-chelating ligand for Cu(II),<sup>1</sup> and we extended the reactivity of malonamides to include the step growth synthesis of polymalonates.<sup>2</sup> As a consequence we were intrigued by the further potential of the malonamide motif and whether its novel use as a ligand could be developed for important catalytic transformations. To the best of our knowledge this class of simple copper (I) *O,O*-chelate have never been used in a catalytic process;<sup>3</sup> this is somewhat surprising given the levels of steric and electronic variance that can be achieved along with the flexibility to ligate as a neutral donor or as an ionic donor (analogous to the ubiquitous *acac* motif). The tuneable nature of this pro-ligand makes it ideal for catalysis. We herein report our initial results in this area, where Cu(I) malonamide complexes have been synthesised and their catalytic competency in azide-alkyne cycloaddition reactions studied, both for the synthesis of small organic triazoles and in the step growth cycloaddition synthesis of oligo(triazoles).

The azide-alkyne cycloaddition reaction (or Huisgen 1,3-dipolar cycloaddition reaction) is undoubtedly of universal importance, being exploited under exacting 'click' conditions in the synthesis of small organic motifs, with 1,4-regioselectivity being observed preferentially using copper catalysts.<sup>4</sup> The utility of this reaction is further highlighted in the synthesis of poly(triazoles) for use in polymer chemistry and materials science.<sup>5</sup> The transformation has also found applications in medicinal chemistry and biochemistry.<sup>6</sup> Given the prevalence and importance of this transformation, we

opted to test the potential of our new complexes in these cycloadditions.

## Results and discussion

We initiated our research by synthesising a small library of pro-ligands with a range of steric and electronic properties. This was achieved in generally good yields (up to 56%) and on a large scale (up to 0.1 mol). Two principal routes can be used; due to steric hindrance, **1** can only be accessed using Mukaiyama's reagent to couple malonic acid to diisopropylamine<sup>7</sup> (Scheme 1a) whereas synthesis of **2** to **4** is possible using aminolysis,<sup>8</sup> by reacting dimethylmalonate with the appropriate amine (Scheme 1b).

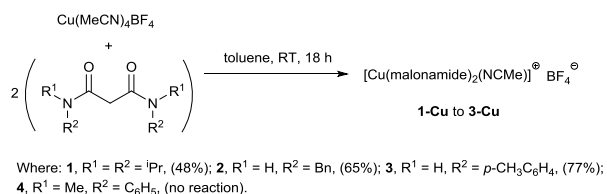


**Scheme 1.** Pro-ligand synthesis using Mukaiyama's reagent or aminolysis.

Reaction of the pro-ligands with [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> gives the desired Cu(I) complexes (**1-Cu** to **3-Cu**) in high yield as lilac solids (Scheme 2). These solids are air stable in the solid state for several days but become air-sensitive when suspended in solvent or with prolonged exposure to moisture in the atmosphere. Use of **4** as a ligand results in decomposition and precipitation of a black nano-particulate side-product. No copper complex was isolated. This is presumably due to steric hindrance limiting product formation, reflecting the poor yield obtained when preparing the pro-ligand, **4**. Elemental analysis of **1-Cu**, **2-Cu** and **3-Cu** indicates the presence of one MeCN per metal centre. The Cu(I) complexes (**1-Cu** to **3-Cu**) are insoluble in standard deuterated solvents and thus the chemical composition is proven by elemental analysis and by controlled oxidation to the Cu(II) congener

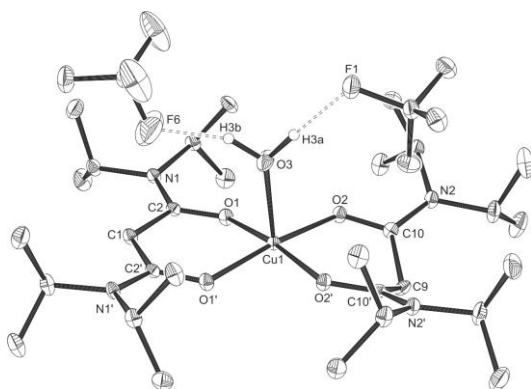
<sup>a</sup> Department of Chemistry, University of Bath, Claverton Down, Bath, UK. BA2 7AY  
Email: r.l.webster@bath.ac.uk  
Electronic Supplementary Information (ESI) available: analysis data for all products. See DOI: 10.1039/x0xx00000x

(**5**, **6** and **7** respectively) by exposure to air and then recrystallisation in  $\text{CH}_2\text{Cl}_2$ /pentane or THF/pentane to yield the requisite Cu(II) malonamide complexes. Conversion from Cu(I) to the pale blue-turquoise Cu(II) complexes occurs in moderate yield (11 to 47%), where the yield is limited to 50% due to sequestration of an extra  $\text{BF}_4^-$  anion to allow oxidation. Presumably the remaining copper disproportionates into Cu(0), similar to observations made by Lei and co-workers on the disproportionation of Cu(I)  $\beta$ -keto enolate analogues.<sup>9</sup>



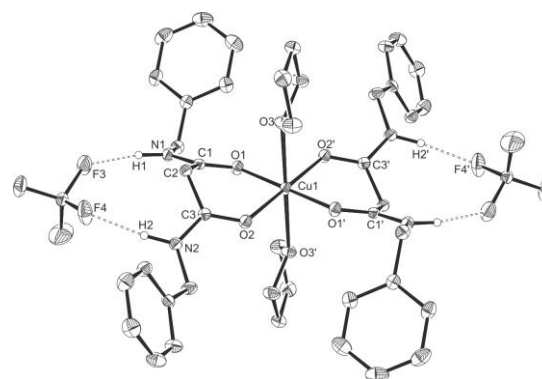
**Scheme 2.** Synthesis of Cu(I) complexes **1-Cu** to **3-Cu**.

Complex **5**<sup>10</sup> exists in a square pyramidal geometry in the solid state. Crystallisation in hydrous solvent allows ligation of  $\text{H}_2\text{O}$  to the metal centre, which is subsequently able to hydrogen bond to both  $\text{BF}_4^-$  counterions. An interesting feature of this Cu(II) complex is the ring-puckering at C9, which is not observed at C1; this ring maintains an almost planar geometry around the metal-centre. Ring puckering at C9 results in a narrow C10-C9-C10 bond angle ( $112.3(3)^\circ$ ) and widening of the O2-Cu-O2 angle ( $92.47(7)^\circ$ ) compared to the planar ring which exhibits an angle of  $118.2(3)^\circ$  around C1 and a close to right-angle connectivity for O1-Cu-O1 ( $89.28(7)^\circ$ ).



**Fig. 1.** Structure of complex **5**, formed in 47% yield from **1-Cu**. Selected bond lengths (Å): Cu-O1 1.936(2), Cu-O2 1.947(2), Cu-O3 2.217(3), O1-C2 1.256(3), O2-C10 1.258(3), N1-C2 1.330(3), N2-C10 1.322(3). Selected bond angles ( $^\circ$ ): O1-Cu-O1 89.28(7), O2-Cu-O2 92.47(7), C2-C1-C2 118.2(3), C10-C9-C10 112.3(3). Disorder and carbon bound hydrogen atoms omitted for clarity. Primed labels related to those in the asymmetric unit by the  $-x, -y, -z$  symmetry operation. Thermal ellipsoids set at the 30% probability level.

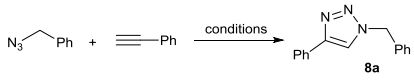
Complex **6**<sup>11</sup> is obtained from a wet THF/pentane recrystallising solution and in contrast to **5**, preferential ligation of THF is observed. An octahedral geometry around the metal centre is obtained, with THF coordinating in the axial positions. The  $\text{BF}_4^-$  counter ions are, once again, involved in hydrogen bonding, however, in this case they interact with the N-H protons on the ligand. Both six-membered cupracycles exhibit ring-puckering.



**Fig. 2.** Structure of complex **6**, formed in 16% yield from **2-Cu**. Selected bond lengths (Å): Cu-O1 1.947(1), Cu-O2 1.977(1), C1-N1 1.318(2), C3-N2 1.315(3), Cu-O3 2.378(2). Selected bond angles ( $^\circ$ ): O1-Cu-O2 92.16(6), C1-C2-C3 109.9(2). Carbon bound hydrogen atoms omitted for clarity. Primed labels related to those in the asymmetric unit by the  $-x, 1-y, -z$  symmetry operation. Thermal ellipsoids set at the 30% probability level.

With our Cu(I) malonamide complexes, **1-Cu**, **2-Cu** and **3-Cu** in hand we began to explore their synthetic utility as catalysts in the azide-alkyne cycloaddition reaction. We started our investigation in this area by comparing the reactivity of **1-Cu**, **2-Cu** and **3-Cu** in the azide-alkyne cycloaddition of phenylacetylene and benzylazide (Table 1). The control experiments gave very poor yields of cycloaddition product (compare Entries 1 to 4). With 2.5 mol% loading of pre-catalyst **1-Cu** we observe 87% spectroscopic yield of the cycloaddition product (**8a**) after one hour at RT. This is modest in comparison to other 1,3-dipolar cycloaddition reactions under neat conditions,<sup>4</sup> where state-of-the-art examples using a Cu(I) complex as the pre-catalyst include, but are not limited to, highly active NHC systems developed by Nolan,<sup>12</sup> Sarkar's abnormal NHC systems<sup>13</sup> and Díez-González's phosphine-based pre-catalyst.<sup>14</sup> Using **1-Cu** as the pre-catalyst, the reaction has an initial turnover frequency of  $167 \text{ h}^{-1}$  for the first five minutes of the reaction, which drops to  $60 \text{ h}^{-1}$  after 25 minutes and after 40 minutes the reaction is incredibly sluggish, with little turnover observed. Reaction monitoring under an inert atmosphere in  $\text{C}_6\text{D}_6$  for ease of NMR studies shows that the reaction is much slower in this solvent (only 10% complete after 1 h at RT using 2.5 mol% **1-Cu**). Stirring is also vital for the reaction to proceed; in an NMR tube saturation kinetics are observed when the catalyst loading is increased to 3.75 mol%.

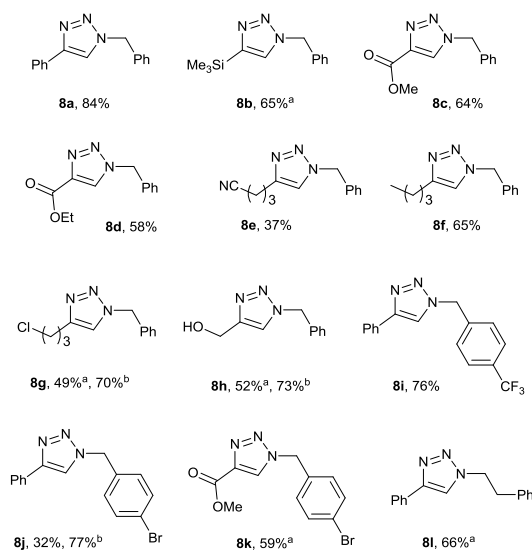
When the benzyl adduct **2-Cu** is used in neat conditions, only 55% spectroscopic yield is obtained and 43% with the aniline-derived complex, **3-Cu** (Table 1, Entries 5 and 6). Pleasingly, the reaction can also be carried out on water (Entry 7) and *in situ* catalyst preparation continues to give modest yield of product (Entry 8). *In situ* reduction of the air-stable Cu(II) congener, **5**, using sodium ascorbate<sup>15</sup> gives 21% **8a** after 1 h at RT and 69% after 4 h at RT (Entry 9), thus offering a viable alternative to the air-sensitive handling conditions required when using the Cu(I) pre-catalysts.

**Table 1.** Optimisation of azide-alkyne cycloaddition.


Entry	Pre-catalyst	Conditions	Spec. Yield <b>8a</b> , % <sup>a</sup>
1	Cu-free	-	trace
2	Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	2.5 mol%	12
3	<b>1</b>	5 mol%	trace
4	<b>1-Cu</b>	2.5 mol%	87 (84)
5	<b>2-Cu</b>	2.5 mol%	55
6	<b>3-Cu</b>	2.5 mol%	43
7 <sup>b</sup>	<b>1-Cu</b>	2.5 mol%, H <sub>2</sub> O	76
8	<b>1</b> + Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	5 mol% <b>1</b> , 2.5 mol% [Cu]	51
9	<b>5</b> + Na ascorbate	2.5 mol% [Cu], 25 mol% [Na]	15, 69 <sup>c</sup>

General reaction conditions: benzylazide (63  $\mu$ L, 0.5 mmol), phenylacetylene (50  $\mu$ L, 0.5 mmol), 1 h, RT, N<sub>2</sub>. <sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,2-DCE as an analytical standard (isolated yield shown in brackets). <sup>b</sup>Degassed H<sub>2</sub>O, performed under N<sub>2</sub>. <sup>c</sup>4 h, RT.

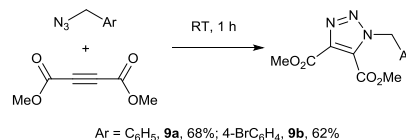
Using pre-catalyst **1-Cu**, a range of alkynes are tolerated in this transformation (Figure 3) including propiolates (**8c** and **8d**), nitriles (**8e**), unactivated alkynes (**8f**) and halo-substituted alkynes (**8g**). The azide coupling partner can also be varied (**8i**, **8j**, **8k** and **8l**) and all reactions can still be undertaken at RT with only a modest increase in reaction time necessary in some cases. Synthesis of **8c** and **8k** can be achieved thermally in the absence of **1-Cu**; heating at 70 °C for 1 h gives 68% and 21% of **8c** and **8k** respectively. However, no reaction is observed in the absence of a catalyst after 3 h at RT.



**Fig. 3.** Substrate scope for azide-alkyne cycloaddition reaction using complex **1-Cu**. Reaction conditions: azide (0.5 mmol), alkyne (0.5 mmol), **1-Cu** (2.5 mol%, 8 mg), RT, 1 h, N<sub>2</sub> isolated yield. <sup>a</sup>3h, RT. <sup>b</sup>24h, RT.

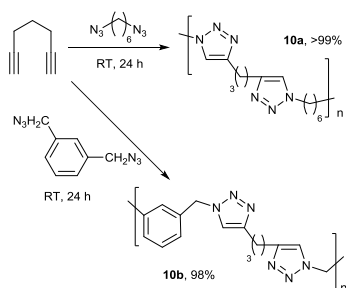
We then proceeded to investigate alkenes and the potential of reacting more challenging alkynes. Unfortunately reaction of styrene with benzyl azide in the presence of 2.5 mol% **1-Cu**, even at 60 °C for 24 h, shows only unreacted starting materials by <sup>1</sup>H NMR. Likewise, activated alkenes such as methyl- and butylacrylate do not react

even with prolonged heating at 60 °C. No reaction is observed with the internal alkyne methyl-2-butyrate, however, dimethylacetylene dicarboxylate does give good yield of the corresponding triazole after 1 h at RT.<sup>16</sup> It should be noted that this transformation is in fact not a catalytic one and the cycloaddition occurs readily at RT catalyst-free (Scheme 3).<sup>17</sup> In the presence of 2.5 mol% **1-Cu**, 73% **9a** and 61% **9b** is obtained.



**Scheme 3.** Cycloaddition of internal alkyne dimethylacetylene dicarboxylate. Reaction conditions: azide (0.5 mmol), alkyne (0.5 mmol), RT, 1 h, N<sub>2</sub>.

Finally the competency of **1-Cu** at catalysing the polymerisation of diazides and diynes was explored (Table 2). The oligomeric pre-polymers are insoluble in organic solvents but DSC analysis shows that both products have good thermal stability, where **10b** has a *T<sub>g</sub>* of 80.1 °C and a *T<sub>m</sub>* of 248.4 °C. In comparison **10a** has a much reduced *T<sub>g</sub>* (18.1 °C), but this is contrasted by a high *T<sub>m</sub>* of 283.2 °C. Analysis by MALDI-ToF indicates both products form pre-polymer with very similar molecular weights (1,800 g mol<sup>-1</sup>). This is the first time these oligo(triazole) structures have been reported and we are currently investigating the potential of high molecular weight polymer synthesis through vacuum condensation and subsequent post-polymerisation functionalisation.

**Table 2.** Oligo(azide-alkyne) cycloaddition to give products **10a** and **10b**.


Property	<b>10a</b>	<b>10b</b>
<i>M<sub>n</sub></i> (g mol <sup>-1</sup> ) <sup>a</sup>	1800	1800
PDI <sup>a</sup>	1.06	1.07
DP	6	7
<i>T<sub>g</sub></i> (°C) <sup>b</sup>	18.1	80.1
<i>T<sub>m</sub></i> (°C) <sup>b</sup>	283.2	248.4
<i>T<sub>c</sub></i> (°C) <sup>b</sup>	-	188.5, 207.4

Measurements: <sup>a</sup>MALDI-ToF. <sup>b</sup>DSC.

## Conclusions

In summary, we have presented initial investigations into the use of the malonamide motif as a neutral ligand in Cu(I) catalysis. The complexes prepared prove to be competent pre-catalysts for the synthesis of triazoles using azide-alkyne cycloaddition methodology. The Cu(I) complexes are readily oxidised in hydrous solvent to furnish the Cu(II) analogues in good yield. Catalysis with the Cu(I) complexes has also been extended to include preliminary studies in oligo(azide-alkyne) cycloadditions, with the pre-polymers prepared demonstrating good thermal stability and in one case a high *T<sub>g</sub>* of 80.1 °C is observed. Overall, we have demonstrated that the malonamide is a good ligand for copper catalysis and hints at the potential of this ligand in other transformations, where we envisage that it could be further exploited as neutral donor or developed as

an anionic ligand similar to the ubiquitous *acac* motif; these studies are on-going.

## Experimental

### General considerations

Reagents were purchased from Sigma Aldrich and used without further purification. Laboratory grade solvents were purchased from Fisher Scientific and used without further purification. NMR data was collected at 250, 300, 400 or 500 MHz on Bruker instruments in CDCl<sub>3</sub> at 298 K and referenced to residual protic solvent. Heated and anhydrous reactions were undertaken in Schlenk tubes or J-Young reaction tubes.

### Method for the preparation of 1.

NEt<sub>3</sub> (1 mL, 7.17 mmol) followed by diisopropylamine (1 mL, 7.14 mmol) each in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added dropwise to a stirred solution of malonic acid (312 mg, 3 mmol, 1 eq) and Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide, 1.61 g, 6.3 mmol, 2.1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at 0 °C. The solution was left to stir at 0 °C for 30 minutes and then allowed to warm to RT and stirred for a further 4 hours. The resulting mixture was concentrated *in vacuo* and the product was isolated by silica gel column chromatography (40% EtOAc/pentane). White solid, 332 mg (41%). <sup>1</sup>H NMR (400 MHz; 298 K; CDCl<sub>3</sub>) δ 4.32 (septet, 2H, *J* 6.8 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 3.40 (s, 2H, CH<sub>2</sub>), 1.39 (s, 12H, *J* 6.8 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 1.16 (d, 12H, *J* 6.8 Hz, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz; 298 K; CDCl<sub>3</sub>) δ 165.8 (C=O), 49.4 (C(O)CH<sub>2</sub>C(O)), 46.0 (CH(CH<sub>3</sub>)<sub>2</sub>), 20.6 (CH(CH<sub>3</sub>)<sub>2</sub>), 20.3 (CH(CH<sub>3</sub>)<sub>2</sub>); IR (solid) ν 2962, 1734, 1614 cm<sup>-1</sup>; m.p. 146 °C.

### Method for the preparation of 2.

Dimethyl malonate (5.7 mL, 50 mmol, 1 eq) and benzylamine (10.9 mL, 100 mmol, 2 eq) were added to a round bottomed flask, heated to 160 °C and stirred for 18 hours with distillation of methanol using short-path distillation apparatus. The product crystallised on cooling, it was then filtered, washed with ice cold ethyl acetate and dried under vacuum. The same protocol can be used to prepare ligands **3** and **4**.

**2:** White solid, 7.87 g (56%). <sup>1</sup>H NMR (250 MHz; 298 K; CDCl<sub>3</sub>) δ 7.38–7.26 (m, 12H, ArH), 4.45 (s, 4H, CH<sub>2</sub>Ar), 1.39 (s, 2H, CH<sub>2</sub>), 1.16 (d, 12H, *J* 6.8 Hz, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (63 MHz; 298 K; CDCl<sub>3</sub>) δ 167.3 (C=O), 137.7 (Ar<sub>q</sub>), 128.6 (Ar), 127.6 (Ar), 127.4 (Ar), 43.5 (CH<sub>2</sub>Ar), 42.9 (C(O)CH<sub>2</sub>C(O)); IR ν 3281, 3064, 3033, 1655, 1624, 1542 cm<sup>-1</sup>; m.p. 144 – 145 °C.

**3:** White solid, 5.89 g (21%). Sparingly soluble in CDCl<sub>3</sub>. <sup>1</sup>H NMR (250 MHz; 298 K; CDCl<sub>3</sub>) δ 8.74 (br. s, 2H, NH), 7.57 (d, 4H, *J* 7.6 Hz, ArH), 7.36 (d, 4H, *J* 7.6 Hz, ArH), 3.54 (s, 2H, CH<sub>2</sub>), 1.58 (s, 6H, CH<sub>3</sub>); IR ν 3268, 3150, 3115, 1645, 1596 cm<sup>-1</sup>; m.p. 231 °C.

**4:** Solid, 2.82 g (10%). <sup>1</sup>H NMR (300 MHz; 298 K; CDCl<sub>3</sub>) δ 7.38–7.32 (m, 6H, ArH), 7.04 (dd, 4H, *J* 7.9, 2.1 Hz, ArH), 3.23 (s, 6H, CH<sub>3</sub>), 3.00 (s, 2H, CH<sub>2</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (63 MHz; 298 K; CDCl<sub>3</sub>) δ 167.1 (C=O), 143.5 (Ar<sub>q</sub>), 129.5 (Ar), 127.8 (Ar<sub>q</sub>), 127.2 (Ar), 41.2 (C(O)CH<sub>2</sub>C(O)), 37.13 (CH<sub>3</sub>); IR ν 3064, 2941, 1644, 1593, 1494 cm<sup>-1</sup>; m.p. 108 °C.

### General method for the synthesis of Cu(I) complexes.

For example, complex **1-Cu**: manipulations carried out under an inert atmosphere. [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> (200 mg, 0.64 mmol, 1 eq), diisopropyl malonamide **1** (343 mg, 1.27 mmol, 2 eq) and toluene (2 mL) were combined in a J-Young reaction tube and stirred at room temperature for 3 hours. Using a metal cannula with a glass paper frit, the reaction solution was filtered away from the precipitate leaving a lilac solid which was then washed with toluene (3 x 1 mL). The solid was then dried under vacuum before storing in a glovebox. See ESI for analytical data.

### General procedure for the synthesis of triazoles **8a** to **8l** and **9a** and **9b**.

Alkyne (0.5 mmol) was added to azide (0.5 mmol) and the appropriate copper malonamide complex (2.5 mol%) in a small Schlenk tube and stirred for one hour at room temperature. The reaction was quenched with water and the product extracted into EtOAc. The extractions were filtered through a pipette fitted with glass paper and MgSO<sub>4</sub> before being dried under nitrogen. 1,2-DCE (0.5 mmol) was then added to optimisation reactions for the synthesis of **8a** and the sample analysed by <sup>1</sup>H NMR prior to purification. Spectroscopic yield was obtained by integrating the CH<sub>2</sub> product peak relative to 1,2-DCE. Products could be isolated recrystallisation from EtOAc/pentane as necessary. See ESI for analytical data. The procedure to synthesise **9a** and **9b** was identical, but can be carried out in the absence of catalyst.

### General procedure for the step growth synthesis of **10a** and **10b**.

Diyne (0.5 mmol) was added to diazide (0.5 mmol) and the appropriate copper malonamide complex (2.5 mol%) in a small Schlenk tube and stirred for one hour at room temperature to give low *M<sub>n</sub>* pre-polymer. The pre-polymer was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 2 mL) followed by MeOH (2 x 2 mL), before drying under a stream of N<sub>2</sub>. Analysis by of the sample by carried out using MALDI-ToF, with the sample loaded as a solid.

## Acknowledgements

We thank the Royal Society of Chemistry for an Undergraduate Summer Research Bursary (SJB) and the University of Bath for additional financial support.

## Notes and references

- 1) a) Bull, W. E.; Ziegler, R. G. *Inorg. Chem.* 1966, **5**, 689; b) El-Asmy, A.; Al-Ansi, T.; Amin, R.; El-Shahat, F. M. *Transition Met. Chem.* 1990, **15**, 12; c) De Beukeleer, S.; Desseyn, H.; Perlepes, S.; Manessi-Zoupa, E. *Transition Met. Chem.* 1994, **19**, 468; d) Simonsen, O.; la Cour, A. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* 1995, **51**, 2006; e) Singh, B.; Singh, V. L. *Indian J. Chem. Sect. A* 1999, **38A**, 609; f) Rodríguez-Martín, Y.; Lorenzo Luis, P. A.; Ruiz-Pérez, C. *Inorg. Chim. Acta* 2002, **328**, 169; g) Bjernemose, J. K.; McKenzie, C. J.; Raithby, P. R.; Teat, S. J. *Dalton Trans.* 2003, 2639; h) Ershov, M. A.; Skvortsov, V. G.; Pilchikova, Y. Y.; Koltsova, O. V.; Suponitsky, K. Y. *Acta Crystallogr. Sect. E: Struct. Rep. Online* 2006, **62**, m3073; i)

- Ershov, M. A.; Skvortsov, V. G.; Pilchikova, Y. Y.; Suponitsky, K. Y. *Acta Crystallogr. Sect. E: Struct. Rep. Online* 2006, **62**, m1181; j) Wang, Y.; Li, F.; Xu, L.; Jiang, N.; Liu, X. *Dalton Trans.* 2013, **42**, 5839; k) Evans, V.; Mahon, M. F.; Webster, R. L. *Tetrahedron* 2014, **70**, 7593.
- 2) Tyler, S. N. G.; Webster, R. L. *Chem. Commun.* 2014, **50**, 10665.
- 3) Manchanda, V. K.; Pathak, P. N. *Sep. Purif. Technol.* 2004, **35**, 85.
- 4) a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, **40**, 2004; b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* 2008, **108**, 2952; c) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* 2010, **39**, 1302; d) Liang, L.; Astruc, D. *Coord. Chem. Rev.* 2011, **255**, 2933; e) Uhlig, N.; Li, C.-J. *Chem. Sci.* 2011, **2**, 1241; f) Berg, R.; Straub, B. F. *Beilstein J. Org. Chem.* 2013, **9**, 2715; g) Sokolova, N. V.; Nenajdenko, V. G. *RSC Adv.* 2013, **3**, 16212; h) Najera, C.; Sansano, J. M. *J. Organomet. Chem.* 2014, **771**, 78.
- 5) a) Binder, W. H.; Kluger, C. *Curr. Org. Chem.* 2006, **10**, 1791; b) Lutz, J.-F. *Angew. Chem. Int. Ed.* 2007, **46**, 1018; c) Chassaing, S.; Sido, A. S. S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. *Chem. Eur. J.* 2008, **14**, 6713; d) Johnson, J. A.; Finn, M. G.; Koberstein, J. T.; Turro, N. J. *Macromol. Rapid Commun.* 2008, **29**, 1052; e) Meldal, M. *Macromol. Rapid Commun.* 2008, **29**, 1016; f) van Dijk, M.; Rijkers, D. T. S.; Liskamp, R. M. J.; van Nostrum, C. F.; Hennink, W. E. *Bioconjugate Chem.* 2009, **20**, 2001; g) Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* 2010, **39**, 2522; h) Chu, C.; Liu, R. *Chem. Soc. Rev.* 2011, **40**, 2177; i) Astruc, D.; Liang, L.; Rapakousiou, A.; Ruiz, J. *Acc. Chem. Res.* 2012, **45**, 630.
- 6) a) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* 2007, **36**, 1674; b) Gramlich, P. M. E.; Wirges, C. T.; Manetto, A.; Carell, T. *Angew. Chem. Int. Ed.* 2008, **47**, 8350; c) Lutz, J.-F.; Zarafshani, Z. *Advanced Drug Delivery Reviews* 2008, **60**, 958; d) Glaser, M.; Robins, E. G. *Journal of Labelled Compounds & Radiopharmaceuticals* 2009, **52**, 407; e) El-Sagheer, A. H.; Brown, T. *Chem. Soc. Rev.* 2010, **39**, 1388; f) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* 2011, **6**, 2696; g) Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res.* 2011, **44**, 666; h) Hou, J.; Liu, X.; Shen, J.; Zhao, G.; Wang, P. G. *Expert Opinion on Drug Discovery* 2012, **7**, 489; i) Avti, P. K.; Maysinger, D.; Kakkar, A. *Molecules* 2013, **18**, 9531; j) Fuaad, A. A. H. A.; Azmi, F.; Skwarczynski, M.; Toth, I. *Molecules* 2013, **18**, 13148; k) Li, H.; Aneja, R.; Chaiken, I. *Molecules* 2013, **18**, 9797; l) Pretze, M.; Pietzsch, D.; Mamat, C. *Molecules* 2013, **18**, 8618; m) Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. *Eur. J. Org. Chem.* 2014, **2014**, 3289.
- 7) Hutchby, M.; Houlden, C. E.; Haddow, M. F.; Tyler, S. N. G.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* 2012, **51**, 548.
- 8) a) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* 1974, **96**, 7018; b) Siliphaivanh, P.; Harrington, P.; Witter, D. J.; Otte, K.; Tempest, P.; Kattar, S.; Kral, A. M.; Fleming, J. C.; Deshmukh, S. V.; Harsch, A.; Secrist, P. J.; Miller, T. A. *Bioorg. Med. Chem. Lett.* 2007, **17**, 4619.
- 9) Cheng, B.; Yi, H.; He, C.; Liu, C.; Lei, A. *Organometallics* 2015, **34**, 206.
- 10) Crystal data for  $C_{30}H_{62}B_2CuF_8N_4O_5$ , **5**:  $M = 796.00$ ,  $\lambda = 1.54184$  Å, orthorhombic, space group  $Cmc2_1$ ,  $a = 21.1798(2)$ ,  $b = 12.69988(12)$ ,  $c = 14.89542(16)$  Å,  $U = 4006.58(7)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.320$  g cm<sup>-3</sup>,  $\mu = 1.446$  mm<sup>-1</sup>,  $F(000) = 1684$ . Crystal size =  $0.19 \times 0.11 \times 0.04$  mm, unique reflections = 3909 [ $R(\text{int}) = 0.0583$ ], observed reflections [ $I > 2\sigma(I)$ ] = 3822, data/restraints/parameters = 3909/28/274. Observed data;  $R1 = 0.0410$ ,  $wR2 = 0.1043$ . All data;  $R1 = 0.0419$ ,  $wR2 = 0.1058$ . Max peak/hole =  $0.0502$  and  $-0.438$  eÅ<sup>-3</sup>, respectively. CCDC 1050824.
- 11) Crystal data for  $C_{21}H_{26}BCu_{0.50}F_4N_2O_3$ , **6**:  $M = 473.02$ ,  $\lambda = 1.54184$  Å, triclinic, space group  $P-1$ ,  $a = 9.6068(3)$ ,  $b = 10.6220(4)$ ,  $c = 11.5052(5)$  Å,  $\alpha = 79.821(3)^\circ$ ,  $\beta = 77.423(3)^\circ$ ,  $\gamma = 73.676(3)^\circ$ ,  $U = 1091.27(7)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_c = 1.440$  g cm<sup>-3</sup>,  $\mu = 1.454$  mm<sup>-1</sup>,  $F(000) = 491$ . Crystal size =  $0.22 \times 0.15 \times 0.13$  mm, unique reflections = 4254 [ $R(\text{int}) = 0.0326$ ], observed reflections [ $I > 2\sigma(I)$ ] = 3948, data/restraints/parameters = 4254/2/294. Observed data;  $R1 = 0.0478$ ,  $wR2 = 0.1321$ . All data;  $R1 = 0.0504$ ,  $wR2 = 0.1356$ . Max peak/hole =  $0.627$  and  $-0.413$  eÅ<sup>-3</sup>, respectively. CCDC 1050825.
- 12) a) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* 2006, **12**, 7558; b) Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* 2008, **47**, 8881; c) Díez-González, S.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, A. M. Z.; Nolan, S. P. *Dalton Trans.* 2010, **39**, 7595.
- 13) Hohloch, S.; Su, C.-Y.; Sarkar, B. *Eur. J. Inorg. Chem.* 2011, **2011**, 3067.
- 14) Lal, S.; Díez-González, S. *J. Org. Chem.* 2011, **76**, 2367.
- 15) a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* 2002, **41**, 2596; b) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* 2005, **127**, 210.
- 16) This transformation can be undertaken catalyst-free (Ref. 17), but has been reported in the presence of a catalyst: a) Lee, B.-H.; Wu, C.-C.; Fang, X.; Liu, C. W.; Zhu, J.-L. *Catal. Lett.* 2013, **143**, 572; b) Sau, S. C.; Roy, S. R.; Sen, T. K.; Mullangi, D.; Mandal, S. K. *Adv. Synth. Catal.* 2013, **355**, 2982; c) S. Ding, G. Jia and J. Sun, *Angew. Chem. Int. Ed.* 2014, **53**, 1877; d) Jacob, K.; Stolle, A. *Synth. Commun.* 2014, **44**, 1251.
- 17) For previous reports on the catalyst-free reaction see: a) L'Abbé, G.; Galle, J. E.; Hassner, A. *Tetrahedron Lett.* 1970, **11**, 303; b) Honda, K.; Nakanishi, H.; Nagawa, Y.; Yabe, A. *J. Chem. Soc., Chem. Commun.* 1984, 450; c) J. Hagan, D.; Chan, D.; H. Schwalbe, C.; F. G. Stevens, M. *J. Chem. Soc., Perkin Trans. 1* 1998, 915.